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L3: Entry 8 of 9

File: USPT

Jun 29, 1993

DOCUMENT-IDENTIFIER: US 5223248 A

TITLE: Non-antibacterial tetracycline compositions possessing antiplaque properties

Abstract Text (1):

A method of inhibiting plaque formation on mammalian tooth surfaces is disclosed. The method includes contacting the tooth surfaces with an effective amount of a non-antibacterial tetracycline. In a preferred embodiment, such tetracyclines are included in various oral hygiene products such as dentifrices, lozenges, chewing gums and the like to contact the tooth surfaces and prevent plaque accumulation thereon.

Brief Summary Text (2):

The present invention relates to methods of inhibiting plaque formation on hard and soft tissue surfaces. In particular, the present invention relates to preventing dental plaque formation using non-antibacterial tetracyclines.

Brief Summary Text (3):

For several decades now, there has been an increased awareness of the relationship between plaque formation on tooth surfaces and dental cavities or caries. Dental plaque is generally regarded as a film of bacteria, bacterial polymers, salivary polymers, remnants of epithelial cells and leukocytes. The bacteria, principally *Streptococcus mutans*, is part of the naturally occurring microflora of the oral cavity. The bacteria use natural sugars such as sucrose and glucose included in the diet as a nutrition source and produce cement-like polymers which bind to the enamel tooth surface. Once bound, the opportunistic bacteria cause demineralization of the enamel by secreting acids and ultimately caries. Although the roots of teeth lack enamel, plaque formation may also be found below the gingival margin. Such plaque formation ultimately leads to root caries, a leading cause of tooth loss in adults. Root caries can be especially prevalent when, due to periodontal disease, the gums and alveolar bone both recede and expose the roots.

Brief Summary Text (4):

In the past, most efforts aimed at reducing plaque formation and dental caries have included reducing sugar intake, regular brushing, flossing and periodic removal of the plaque by dental professionals.

Brief Summary Text (5):

In some cases, plaque formation on tooth surfaces may become excessive and even pathologic. In these situations, it is often necessary to institute prophylactic measures in addition to those described above. In the past, broad spectrum antibiotics such as tetracyclines and metronidazole have been used in the treatment of periodontal disease to reduce oral cavity microflora, which is the most virulent aspect of plaque formation. Although antibiotic agents are effective in reducing the bacteria responsible for plaque formation, extended periods of antibiotic administration are avoided due to high incidences of side effects. Side effects most often associated with long-term antibacterial agent usage include intestinal disturbances, overgrowth of yeast and fungi, and most importantly, the development of antibiotic-resistant bacterial strains.

Brief Summary Text (10):

Although some oral hygiene products such as dentifrices have been recently

introduced to combat the problem of plaque formation, a complete solution remains elusive.

Brief Summary Text (11):

In view of the desire to reduce plaque formation on tooth surfaces and further in view of the desire to avoid using antimicrobial antibiotics to accomplish this result, it is an object of the present invention to provide an improved method of inhibiting plaque formation on tooth surfaces.

Brief Summary Text (12):

It is a further object of the present invention to provide a method of inhibiting plaque formation on tooth surfaces using non-antibacterial tetracyclines.

Brief Summary Text (14):

In accordance with the present invention, it has been surprisingly found that tetracyclines inhibit plaque formation on tooth surfaces in a manner completely separate from antibacterial eradication of the oral cavity microflora. The method includes contacting the tooth surfaces with an effective amount of a non-antimicrobial tetracycline which results in the prevention of plaque formation and colonization on tooth surfaces.

Brief Summary Text (16):

The amount of the non-antimicrobial tetracycline used in the method of the present invention may be generally described as that amount which effectively inhibits plaque formation on tooth surfaces. For example, a non-antimicrobial tetracycline, may be included in dentifrices, mouthwashes or similar oral hygiene preparations in amounts ranging from about 10 mg% to about 100 mg%. In a preferred embodiment, the non-antimicrobial tetracycline is included in amounts of from about 15 mg% to about 25 mg%, with concentrations of about 20 mg% being most preferred. When contacting tooth surfaces at these concentrations and for time periods typical for the oral hygiene product selected to contain the non-antimicrobial tetracycline, the non-antibacterial tetracyclines described herein prevent plaque formation on tooth surfaces. Naturally, the amount of the various tetracycline analogues will vary somewhat from each other and the ranges set forth above are only illustrative of all possible dosage choices. Those skilled in the art will determine optimal concentrations for the desired non-antimicrobial tetracycline from clinical experience in order to carry out the present method.

Brief Summary Text (17):

As a result of the present invention, significant improvements in oral hygiene are realized. By eliminating the adhesion of plaque to tooth surfaces, the destructive activity caused by normal mouth flora is significantly reduced. Moreover, the reduction of plaque formation on tooth surfaces is realized not only on the enamel area above the gingival margin but also on the root surfaces below the gingival margin. Thus, the method of the present invention's prevention of plaque formation on tooth surfaces removes a critical step in the pathologic process of tooth decay. Since the method of the present invention includes non-antimicrobial tetracyclines, the inhibition of plaque formation on tooth surfaces is achieved without using antimicrobial agents. Thus, the oral microflora remains intact. Antimicrobially-resistant strains of organisms, gastrointestinal disturbances, yeast and fungi overgrowth which are associated with antimicrobial therapy are also beneficially avoided.

Drawing Description Text (3):

FIG. 2 is a photograph showing the gum area, gingival margin and lower incisors of an untreated diabetic ODU rat with extensive plaque formation on the incisors and on the gums.

Detailed Description Text (2):

In accordance with the present invention, a method for preventing plaque formation

on tooth surfaces is disclosed. The method includes contacting tooth surfaces with an effective amount of a non-antimicrobial tetracycline which prevents plaque formation.

Detailed Description Text (6):

In accordance with the present invention, the amount of the tetracycline required to inhibit dental plaque formation on tooth surfaces is an amount which is effectively non-antimicrobial yet is effective in inhibiting plaque formation and plaque adhesion on tooth surfaces. The amount of non-antimicrobial tetracycline may also be described as a range. The highest amount is that amount which does not cause clinically detrimental side effects. For the purpose of the present invention, side effects would include any untoward reaction which would clinically warrant ceasing the tetracycline's administration. Such side effects include, for example, symptoms of toxicity. The lowest amount is that minimum amount which produces the desired result of preventing plaque formation on tooth surfaces.

Detailed Description Text (7):

For illustrative purposes, non-antimicrobial tetracyclines may be included in vehicles such as dentifrices, mouthwashes, chewing gums, lozenges, confections or other suitable dental hygiene preparations to carry out the method of the present invention. In such embodiments, the tetracycline may be included in an amount of from about 10 mg% to about 100 mg%. In a preferred embodiment, the non-antimicrobial tetracycline may be present in amount of from about 15 mg% to about 25 mg%. In a most preferred embodiment, the non-antimicrobial tetracycline is present in an amount of about 20 mg%. The method of the present invention may then be carried out by using one of the dental hygiene products described above containing a non-antimicrobial tetracycline to contact the tooth surfaces for a sufficient time to inhibit plaque formation.

Detailed Description Text (8):

The time required for the non-antimicrobial tetracycline to contact the tooth surface and effectively inhibit plaque formation is conveniently the same amount of time as one is accustomed to for using oral hygiene products. For example, if the non-antimicrobial tetracycline is included in a toothpaste, normal brushing one to three times daily is sufficient. Similarly, contacting the teeth with an oral rinse containing the tetracycline for normal periods of around a minute before expectorating one to three times daily would achieve the same result.

Detailed Description Text (9):

Tests were conducted using the method of the present invention's prevention of plaque formation on tooth surfaces. The tests demonstrate the effectiveness and unexpected ability of non-antimicrobial tetracyclines to prevent plaque adhesion on tooth surfaces without antibiotic effect on oral flora.

Detailed Description Text (24):

Referring now to FIG. 1, it can be seen that the non-diabetic control ODU rats showed no detectable plaque accumulation on their lower incisors at or near the gingival margin. As can be seen in FIG. 2, the untreated diabetic ODU rats showed large accumulations of dental plaque on the incisors extending to and including the gingiva. In FIGS. 3-4, it can be seen that the rats in both the antimicrobial and non-antimicrobial tetracycline-treated groups showed significant reductions in plaque accumulation on the lower incisors when compared to the untreated diabetic group. It was also observed that the lower incisors of the rats in the dedimethylamino-tetracycline-treated group greatly resembled those of the non-diabetic control rats which normally do not develop excessive plaque formation on their tooth surfaces.

Detailed Description Text (27):

In this Example, further evidence of non-antimicrobial tetracyclines ability to inhibit plaque formation was demonstrated. Tiles made of polymethylmethacrylate,

which is used for dentures, and has a surface which approximates the enamel of teeth for plaque adherence purposes were selected. Ten tiles were incubated in test tubes with a plaque-forming solution containing sucrose, fresh saliva, K.sup.+ Ca.sup.++, Na.sup.+, Cl.sup.- and F.sup.- ions, a buffer containing Na.sub.2 HP04 7H.sub.2 O NaHC0.sub.3, and a culture of oral cavity microflora obtained from a patient at the University of New York Dental School Clinic at Stony Brook, N.Y. which had been incubated for three days at 37.degree. C. Half of the test tubes were incubated with 20 mg% or 0.02% by weight of 4-dedimethylaminotetracycline to demonstrate its effectiveness against plaque formation, while the other half were maintained as untreated controls. After the 3-day incubation, each tile was removed from the test tube and all non-adherent material was rinsed away with distilled water. The tiles were then air-dried and any bacterial plaque adhering to the tiles was stained by dipping the tiles into a solution of Basic Fuchsin. The amount of stain on the tile provides a direct correlation to plaque formation. Each tile was then destained in a solution of 5% EDTA in 50% 2-propanol. An aliquot of the destaining solution was then measured for light adsorbence at 550 nm in a Spect. 70 colorimeter and compared to an aliquot from the untreated tiles. The results are set forth below in Table 2.

Detailed Description Text (28):

As can be seen from the above Example, the method of the present invention provides significant advantages and improvements in the inhibition of plaque formation on tooth surfaces. Furthermore, by contacting tooth surfaces with an effective amount of a non-antimicrobial tetracycline, bacterial plaque formation can be significantly inhibited in the oral cavity.

Detailed Description Text (30):

In these Examples, various oral hygiene products containing non-antimicrobial tetracyclines are set forth. In each of the products, the term "CMT" is used to designate a chemically modified tetracycline such as a dedimethylamino-tetracycline which essentially lacks antimicrobial activity. Each of the following illustrative products is useful in providing a vehicle for allowing an effective amount of the tetracycline to contact the tooth surface and thereby inhibit plaque formation.

Other Reference Publication (6):

Golub et al., "Low-dose Doxycycline Therapy: Effect on Gingival and Crevicular Fluid Collagenase Activity in Humans", Journal of Periodontal Research, 25, 321-330 (1990).

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L3: Entry 9 of 9

File: USPT

Jan 21, 1992

DOCUMENT-IDENTIFIER: US 5082653 A

TITLE: Anti-plaque compositions comprising a combination of morpholinoamino alcohol and antibiotic

Abstract Text (1):

Compositions having improved anti-plaque and anti-gingivitis activity comprises a synergistic combination of a) a morpholinoamino alcohol, such as 3-(4-propylheptyl)-4-(2-hydroxyethyl)morpholine and b) an antibiotic, such as the aminoglycosides, amphenicols, ansamycins, carbapenems, cephalosporins, cephamicins, monobactams, oxacephems, penicillins, lincosamides, macrolides, polypeptides and tetracyclines.

Brief Summary Text (3):

Octapinol has been tested for its ability to reduce plaque formation and the development of gingivitis by Willard, Edwardsson, Attstrom and Matsson, "The effect of Octapinol on dento-gingival plaque and development of gingivitis", Journal of Periodontal Research, Volume 18, pages 429-437, (1983). Here it is reported that octapinol may prevent the development of plaque. Some adverse side effects of octapinol are its toxicity, lasting bitter taste and its brownish staining of the teeth.

Detailed Description Text (13):

As the morpholinamino alcohols of this invention by themselves have only weak antimicrobial activity, it is critical to the practice of this invention that said morpholinamino alcohols be present in combination with one or more antibiotics. It is the synergistic combination of said morpholinamino alcohol and an antibiotics which provides the compositions of this invention with their improved anti-plaque and anti-gingivitis properties. Without being bound by any theory or mechanism of action, it is believed that these morpholinamino alcohols inhibit key bacterial membrane functions such as carbohydrate uptake, cellular permeability, cell metabolism and cell division. Bacterial cells which are weakened by these morpholinamino alcohols are more effectively eradicated by antibiotic compounds. Thus, compositions of this invention comprising a combination of said morpholinamino alcohols and antibiotics are extremely effective in inhibiting plaque formation and reducing preformed plaque and for treating gingivitis. These compositions have also demonstrated effectiveness in inhibiting acid production by bacteria, such as Streptococcus mutans, and therefore these composition would have anti-caries activity.

Detailed Description Text (18):

The tetracyclines include apicycline, chlortetracycline, clomocycline, demeclocycline, doxycycline, guamecycline, lymecycline, mecloxycline, methacycline, minocycline, oxytetracycline, penimepicycline, pipacycline, rolitetracycline, sancycline, senociclin, tetracycline and the like. Other antibiotics useful according to this invention are nisin, nystatin, tylosin, pimaricin, cycloserine, mupirocin, tuberin, clindamycin, metronidazole, fluorquinolones, nitrofurantoin, rifampin, sulfonamides, trimethoprim, trimethoprim-sulfamethoxazole, cycloserine, ethambutol, ethionamide, isoniazid, pyrazinamide and rifampin.

Other Reference Publication (2):

(1983) "Effect of Some Polyvalent Cations on Plaque Formation in Vivo", Skjorland et al., Scand. J. Dent. Res., vol. 86, pp. 103-107, (1978).